OBSERVATIONS ON AN OUTBREAK OF VARIOLA MAJOR, WITH SPECIAL REFERENCE TO REVACCINATION REACTIONS.

by

JAMES M. KERR, M.B., Ch.B., D.P.H.

Thesis Presented

for the Degree of M.D.

CONTENTS.

OBSERVATIONS ON AN OUTBREAK OF VARIOLA MAJOR, WITH SPECIAL REFERENCE TO REVACCINATION REACTIONS.

Preamble.

In order to comprehend fully the circumstances in which the Gibraltar Outbreak of Variola Major occurred, it is necessary to appreciate the rather peculiar conditions existing on the Rock, during 1944.

A Limestone isthmus, 2 miles long, 1 mile broad and rising steeply to over 1100 ft, Gibraltar is united to Spain by a small area of Neutral Territory. On the declaration of War in Sept., 1939, the frontier was closed and the Crown colony became virtually, an isolated fortress. By 1944 all women and children had been evacuated and the garrison consisted of about 20,000 soldiers, 4000 airmen and 2000 male Gibraltarians. The Naval population fluctuated from 1000 to 5000 according to fleet movements. The entire resident female population was comprised of about 100 WRNS and 30 Nurses of the QAIMNS and Colonial Nursing Service. In addition, up to 10,000 Spanish Nationals of labouring and domestic service type were employed within the Colony, during the daylight hours.

Of necessity, all movements to or from Gibraltar were either by sea or air routes, and until 1945, when the/

the Allied Armies liberated France and a more direct route became available, Gibraltar was the chief link, especially by air, between the United Kingdom and the East. Furthermore, it will be appreciated that during February - April 1944 (i.e. just before the launching of the Second Front) movements through Gibraltar were immense.

Finally it should be realised that during the Small-pox outbreak, the Non-disruption of Essential war effort, the prevention of spread and the protection of the population were of paramount importance, and that the exigencies of war and lack of essential supplies (e.g. Vaccine Lymph), did not permit as detailed and complete an investigation as might have been, had circumstances been different.

The highest medical authority was vested in the Deputy Director of Medical Services (DDMS), RAMC, who was the Governor's representative. Although each Service was responsible for the medical care of its own personnel, it was also responsible to the DDMS. for co-operative action in medical matters, affecting the garrison as a whole. In the capacity of Senior Medical Officer to the Royal Air Force on Gibraltar, I was responsible for the care and medical administration of 4000 Air Force personnel, the supervision of the Aerodrome and Flying-boat base, and/

and the duties of the Airport medical authorities in addition to those of Port Medical Officer when RAF. personnel, alone, were concerned.

The Outbreak.

It was in these circumstances, that, on the 27th Jan. 1944, a naval rating, disembarked from a ship ex Port Said, and while still in the ambulance, was discovered to be suffering from Variola Major, of haemorrhagic type. He was isolated in the Zymotic Hospital and died 4 days later.

On Feb. 15th, an RAMC nursing orderly, also a convalescing patient in the same institution, was found to be similarly infected and there are no grounds for doubt how he contracted the infection, and that he was the vector for those cases occurring within that hospital, for he had broken the quarantine restrictions.

The extension of the outbreak beyond the hospital precincts and the mode of transmission for those cases outside, could not be satisfactorily traced in most instances.

In all, 23 cases occurred, being grouped in the following manner. After a lull of 15 days from the original case, the first wave of contact cases appeared, Eleven in twelve days. A further gap of seven days then preceded the wave of second contact cases, Six in/

in ten days, to be followed later by a single case of the third contact wave.

Appendix I gives a detailed chart.

The picture was complicated, further, by the arrival, from time to time, of ships from the Eastern Mediterranean, with frank cases of Small-pox on board. Four such individuals were disembarked and are included in the total.

The outbreak ceased on the 21st April but would have concluded at least 2 weeks sooner, but for information from Malta, of the arrival there, by sea, of a case ex Gibraltar. Subsequent information suggested that he probably contracted the infection elsewhere, but could have been infectious on the day of departure from the Rock. He is not included in the local statistics, nor were two others, a soldier of the garrison temporarily in North Africa, and an Army Officer, returned to the United Kingdom, incubating the disease, and who, unfortunately, originated an outbreak in Middlesex with eleven cases and three deaths.

The preamble largely explains why the cases occurred exclusively in males, over the age of twenty-one years.

The/

The distribution of the local cases was as follows:

Service.	Number of Cases.	Recovered	Died.
Army	11	8	3
Royal Navy	8	4	3(+1 from other causes.)
Civilians	2	1	1
Merchant Navy	1	1	0
Italian Navy	1	1	0
R.A.F.	Nil.	Nil.	Nil.
Total:	23	15	7 (+1).

Mortality Rate due to Variola Major = 30.4%.

Mortality Rate, including death following operation for Acute Empyema of Gall Bladder = 34.1%

The Vaccination State of the Smallpox Cases.

It is interesting to record that of the 23 cases, 22 were said to have been vaccinated or revaccinated. 13 of these were done in the year of the outbreak and mostly within 14 days of the development of signs. One was inoculated 1 year previously and 3 two years previously. Two more patients were inoculated 3 and 4 years prior to the outbreak while 2 more were protected in late childhood. However, patients' own statements can be misleading.

A search for cicatricial confirmation failed to reveal any evidence of scars in 4 cases, with extremely/

extremely doubtful results in 6 more. Ten showed definite scars of vaccination in infancy but only two of these, cicatricial proof of reprotection. Five of this latter group had been "revaccinated" once and the other five "reprotected" at least twice. Of the remainder two revealed definite scars acquired in childhood, and one, a single scar in 1940.

The Clinical Types of The Cases.

For the detailed particulars of the vaccination states of the patients and for Details of type and severity of the individual cases, I am indebted to Capt. C. Scott-Stewart, R.A.M.C., who was in charge of the Smallpox hospital.

4 of the 23 cases were stated to be Haemorrhagic-Confluent, and one of these is said to have survived. All 3 non-haemorrhagic Confluent cases had a fatal termination while 14 of the 16 Discrete type survived.

Type.	Number	Recovered	Died	Mortality Rate.
Haemorrhagic-Confluent	4	1	3	75%))87.5%
Confluent	3	0	3	100%)
Discrete	16	14	2	12.5%.

Case Number.	Vaccination State	Type.	Severity	Result.
No. I	No history of Successful Vaccination.	Haemorrhagic. Confluent	Very Severe.	Died.
No 2.	1. Infancy. 2. 28. 1. 44. Early Reaction.	Discrete	Mild.	Recovered.
No 3	July. 41. No Scar Seen.	Haemorrhagic Confluent.	Very Severe	Died
No 4.	1. Infancy 4 Scars. 2. 28. 1. 44. Early Reaction 3. 19. 2. 44. ? Early Reaction	Discrete	Mild.	Died (Previously damaged) Heart
No 5.	1. Infancy 4 Scars. 2. 14. 2. 44. ? Early Reaction	Discrete	Mild	Recovered
No 6.	12. 2. 44. ? Early Reaction	Haemorrhagic Confluent	Very Severe.	Died
No 7.	28. 2. 44 no result noted	Haemorrhagic Confluent.	Very Severe	Recovered.
No. 8.	Childhood. 4 Scars.	Discrete	Severe	Recovered.
No 9.	Childhood 3 Scars	Confluent	Very Severe	Died.
No 10.	1940 1. Scar	Confluent.	Very Severe	Died.
No 11.	1. Infancy. 4 Scars 2. 28. 2. 44. ? Early Reaction	Discrete	Mild	Recovered.
No 12.	1. Infancy 4 Scars. 2. 3. 5. 43. Doubtful Scar.	Discrete	Mild	Recovered.
No. 13.	1. Infancy. 4 Scars. 2. Several times in Post Office Service 3. 1942. 1. Scar.	Discrete	Mild	Recovered.
No 14.	18. 2. 44 ? Early reaction	Discrete	Mild	Recovered
No. 15.	1. 1941 No Result apparent 2. 3. 3. 44. ? Early Reaction	Confluent.	Very Severe	Died
No 16.	1. Infancy. 4 Scars 2. 1941. Doubtful Scar 3. 26. 2. 44. ? Early Reaction	Discrete	Mild.	Recovered
No. 17.	1. Childhood 2. 15 & 2. 40. No Result apparent 3. 26. 2. 44. ? Early Reaction	Discrete	Mild	Recovered
No 18.	26. 2. 44. "Two Takes" ~~Early Reaction~~	Discrete	Mild.	Recovered.
No. 19.	28. 2. 44. ? Early Reaction	Discrete	Mild	Recovered.
No. 20.	1942. Early Reaction.	Discrete	Mild	Recovered.
No 21.	1. Childhood. 4 Scars. 2. 23. 2. 44 No Result.	Discrete	Mild.	Died [after operation following acute Empyema of Gall bladder.
No 22.	1. Childhood. Scar 2. 18. 4. 41 No result apparent. 3. 8. 3. 44 No apparent result.	Discrete	Severe	Recovered
No. 23.	1. Childhood. 4 Scars. 2. 1942-1943.-1944 No Scars. 3. 1944. ? Early Reaction	Discrete	Mild	Recovered

It is not intended to submit detailed particulars of the clinical cases as I was not in charge of these patients.

All patients however had a well marked initial illness, sudden in onset, and although individual symptoms varied in severity, headache appeared to be commonest. Shivering, nausea, vomiting, backache, malaise, lassitude, thirst and pyrexia were all complained of. Pyrexia was well marked in the initial stage, with a tendency to remission on the appearance of the true rash.

No prodromal rashes were noted.

The true rash appeared between the 3rd and 6th days of illness and was typical in distribution.

Any modification due to an existing degree of protection was evidenced in a sparceness of the rash and a speeding up of maturation.

Whereas the initial pyrexia was high, that associated with the course of the true rash varied with the degree of pustulation and the toxicity of the patient.

Pain in the site of the lesions was a prominent feature.

During convalescence a number of patients developed boils, a few, conjunctivitis and one unfortunate, an acute empyema of the gall-bladder, from which operative treatment he did not long survive. (Case No.21) He had suffered from a mild attack of discrete/

discrete small-pox. Apart from him, the other fatal cases died on or about the 10th day of illness. Six of these succumbed to confluent small-pox, half of that number being haemorrhagic in type. The last fatality occurred in a man, with a previously damaged heart, who failed to survive a mild attack, discrete in type.

Treatment, in the main, was symptomatic. Although sulphonamide therapy, in total dosage of 20-30 grms, was exhibited in a limited number of cases, there was no evidence to show that such treatment in any way influenced the patients' condition or comfort in any stage of their illness.

The Administrative Control of the Outbreak.

Although each service was responsible for the protection of its own personnel, corporate action was coordinated by the D.D.M.S. R.A.M.C, the Senior Medical Authority on the Rock.

With a view to controlling the outbreak the following measures were instituted.

(1) The isolation, in a special hospital of all small-pox cases.

(2) The vaccination, segregation and surveillance, in a Reception Centre, of all intimate contacts of known cases.

(3)/

(3) The protection of the entire population, by mass vaccination, irrespective of individual vaccination states.

(4) The immediate notification of all points of aerial and sea contact and the introduction of a medical control system on movements to and from Gibraltar.

(5) Legislation by the Colonial Government setting forth the medical requirements to be fulfilled before entry into or departure from Gibraltar, was permitted.

1. At first the smallpox patients were housed in a wing of the Zymotic Hospital, where accommodation was limited. When the total had reached 10 and the outbreak spread beyond the hospital precincts, a Nissen-hutted Camp, on the eastern side of the Rock, was opened, to which new cases were admitted and convalescents transferred. The new site was utilised until the outbreak ceased on April 21st.

2. As cases appeared, a thorough investigation into the source and mode of infection was made, and all known contacts vaccinated and kept under surveillance. Intimate contacts were segregated for 16 days, in an isolated Reception Centre. Only one intimate contact developed a modified attack and he survived.

3. At the outset, only 500 doses of calf lymph were held in Gibraltar with a population of about 30,000. These were used, rightly, in protecting the hospital staff and contacts of cases. A further 1200 doses flown from the Pasteur Institute, Algiers, were similarly expended.

It is regrettable that although the D.D.M.S. signalled the War Office, Whitehall, for the immediate dispatch, by air, of an adequate supply of lymph to protect the entire population, this took more than a week to arrive. This latter decision had been made, in view of the severity of the disease.

Lymph arrived on Feb. 24th and within 2½ days the four R.A.F. medical officers had inoculated their 4000 odd personnel. The R.A.M.C. with five times as many troops and correspondingly more staff completed its quota well within a week, whilst the Naval Medical authorities, with their fluctuating population, took slightly longer. On March 1st, the vaccination of civilians, including the Spanish employees, was commenced and was completed in 7 days.

14 days after completion of mass vaccination no further cases occurred within Gibraltar, although 4 more cases were disembarked from ships, ex. Eastern Mediterranean.

4./

4. As soon as the nature of the outbreak was apparent, all points of aerial contact were informed by Wireless, warned of the inadequate lymph supplies and requested not to route unprotected persons to, or through Gibraltar. This involved notifying the following R.A.F. authorities.

(A) In the United Kingdom: Air Ministry and H.Q. Coastal and Transport Command.

(B) The Headquarters of the Air Forces in North Africa, West Africa, Italy, and the Azores.

In due course the requisite naval, military and civil authorities were informed.

Throughout, due to exigencies of war, movements of certain individuals and troops continued. At the beginning, with inadequate lymph one was unable to revaccinate them. They were "handed on" therefore for vaccination and surveillance to the appropriate receiving medical authority who was warned of their arrival. When lymph became available none were permitted to depart without a valid certificate of successful protection, while arrivals without this document were required to be vaccinated.

Considerable divergence of opinion existed as to the time limits of successful protection and for some inexplicable reason, on 24th Feb. the Governor's Conference decided that vaccination since 1st Feb. constituted this, the decision was at variance with the already declared standard, signalled to all points of/

of aerial contact, who had been informed that a valid certificate constituted evidence of protection "preferably of not less than 14 days and of not more than 1 year's duration."

It was not until March 16th that this latter interpretation was ratified by the Colony's Vaccination Rules, 1944. In the interval the divergence of standards necessitated revaccination, by R.A.F. Control units, of over 900 persons, in transit, by air. This latter checking system had been in operation from the first, and until 24th Feb., when vaccine arrived, merely ensured that points of aerial contact were acting upon instructions. Individuals departing prior to this date carried certificates warning that although not known to have been in contact with small-pox, nevertheless they had come from Gibraltar, where an outbreak existed, and should be vaccinated and kept under surveillance. After this date travellers without valid certificates were vaccinated and if permitted to travel, by exigencies of war, before protection was acquired, were recommended to be kept under surveillance.

Movements: During the period under review (Feb. 19th to April 21st) by air alone, and excluding operational aircrafts and crews, 14,214 passengers of 1823 transport aircraft were "investigated" by Aerodrome and Flying/

Flying boat medical control units, while the port medical authorities had an equally arduous task.

There is no evidence of small-pox having been transmitted to this country by air passenger route, but unfortunately, before the existence of the outbreak was realised, a few days after the original case, an Army officer, convalescent in hospital, returned home, by sea, incubating very modified small-pox and caused the Middlesex Outbreak of 11 cases with 3 deaths.

The Source of Infection and Mode of Transmission.

With reference to the initial outbreak within the bounds of the Zymotic Hospital, investigation revealed beyond any shadow of doubt that the second case was responsible. A Nursing orderly, convalescent, he broke the quarantine restrictions, visited the original case, and as a vector, presumably by infected fomites, transmitted the infection to other patients in his ward. How the disease escaped beyond the hospital bounds was never satisfactorily explained, nor was the source or mode of transmission to most of the subsequent cases. Although it did occur, (Case 14) it was the exception for a new case, first, to have been a known contact.

The following possibilities must be considered:-

(1) Infected Fomites (2) Carriers (3) Air-borne spread. (4) Missed cases.

Despite/

Despite intensive investigations no evidence was brought to light suggesting spread by infected fomites, whilst the possibility of a carrier state seemed more of theoretical consideration than of practical demonstration.

Gibraltar's long axis is virtually North-South with the prevailing wind from the West. The population lived mainly on the western side and northern and southern ends. The cases, however, did not concentrate in any one part, and when the new hospital on the eastern side of the Rock was used, this, in no way, altered the even distribution of the cases.

Transmission of infection by 'Missed cases', was, in my opinion, the likeliest cause. In support of this belief the following personal experience is submitted.

Two months after the outbreak an R.A.F. Officer, returned from North Africa. He had been successfully vaccinated in 1938, (a scar the size of 6d.), and revaccinated in Feb. 1944 with an 'Early or Immediate' result. He complained of intense frontal headache, backache, pyrexia, 103°F., and felt "really ill". Within 4 days the temperature had dropped and this coincided with the appearance of a very sparse macular rash situated mainly on the forehead and even less on the trunk and extremities. This matured to pustulation with some degree of umbilication.

By/

By the 5th day he was feeling comparatively well and was soon ambulatory. On the 10th day he showed a degree of tachycardia which was also noted in the previous cases. The diagnosis of modified small-pox was confirmed by the medical officer in charge of the outbreak cases. The individual had an uneventful convalescence and was left with 26 pock marks. Had not one been alert for the possibility of small-pox such an ambulatory case might well have been missed.

Vaccination.

The decision to vaccinate the entire population having been made, limited supplies of vaccine did not permit the use of more than 2 insertions, which were ¾ inch long and 1 inch apart. Indeed at the onset, not infrequently only one incision was made. This also vetoed the use of heat destroyed vaccine as a control for pseudo, or sensitisation reactions, although such might have proved very instructive. However a simple scratch incision of identical dimensions to those of vaccination was employed successfully as a contrast for traumatic tissue reaction. (See Appendix 2 Photo A.)

Technique:

Arms were washed with soap and water and methylated ether allowed to dry completely before potent lymph was applied. Incisions were made through this into/

into the skin but without drawing blood, and allowed 10 minutes to dry before covering with a simple dressing.

In deciding to review results on the 5th day inclusive, in order to expedite revaccination if necessary, the fact that all R.A.F. personnel had been vaccinated within 5 years was taken into account, for it was anticipated that in the vast majority, reactions would be not only modified in intensity, but accelerated in time. This was a broad ruling to meet operational requirements, but certain selected individuals, revaccinated again, were reviewed at daily intervals.

Bearing in mind that the individuals were R.A.F. men aged 21 to 45 years, all "vaccinated" within 5 years, the following table indicates the findings of revaccination.

Age.	Total.	Type of Reaction		No Reaction
		Vaccinia.	Modified Reaction	
21-45 yrs.	4173	281.	3888.	4.
	(100%)	(6.71%)	(93.12%)	(0.09%)

If the term "Vaccinia" is used to imply a maximum area of reaction between the 8th - 14th days, "Vaccinoid" a maximum area of reaction between the 4th - 7th Days, and "Early" or "Immediate" reaction occurring maximally within the first three days, then the above table can be modified further.

Total	Vaccinia	Vaccinoid	Early Reaction	No Reaction
4173	281	3674	210	4
(100%)	(6.71%)	(88.09%)	(5.03%)	(0.09%)

Vaccinial Reactions.

That 6.7% should show unmodified reactions to revaccination within 5 yrs. may at first sight seem strange. It must be remembered however that little faith could be placed in pay book records, in the absence of demonstrable scars.

The vast majority of vaccinial reactions occurred amongst those with infantile "primaries" and no apparent result on revaccination on entering the service. This, however, does not explain the occurrence of a vaccinial reaction in the presence of scar-formation due to inoculation as recently as 2 and 3 yrs previously. Such cases undoubtedly did occur and photographic proof is submitted in appendix 2. photos. C. and D.

It would appear significant that in the majority of these cases which I saw personally, the reactions under review were first revaccinations in individuals whose original vaccination, performed 2, 3, 4 or 5 yrs. previously, had been a single insertion with resultant scar.

Vaccinoid/

Vaccinoid Reactions.

As was anticipated the vast majority (88.09%) of R.A.F. showed vaccinoid reactions. These results were modified in severity, appeared earlier, reached their maximum between the 4th and 7th days and ran a shorter course, vesicles tending to be smaller and aborted. The early areolar blush with accompanying oedema was less marked. The earlier the day of maximum reaction the more attenuated was the lesion.

"Early" or "Immediate" Reaction.

210 airmen (5%) revealed reactions which were more modified than vaccinoid and which have been described variously as "Early", "Immediate" or "Immune".

The course of vaccination in an unprotected individual is characteristic. After an incubation period of about 3 days, during which nothing is observed, a raised area of redness, then a papule surrounded by an areola of hyperaemia develops. By the 5th day vesiculation has begun and is completed usually by the 7th day. On the 9th day the vesicles have become pustular and scab-formation usually occurs from the 11th day onwards.

In 1898, Cory conducted his well known experiments, and expressed the opinion that the interval elapsing between the inoculation and the day of maximum reaction in /

in revaccination, indicates the measure of immunity to vaccinia. Since then it has been a well recognised fact that where a degree of partial immunity exists from a previous vaccination, subsequent revaccination is characterised by the modified reaction, already described as vaccinoid.

It would appear logical, therefore, to conclude, that in individuals possessing a degree of residual immunity even greater than that of 'vaccinoid' reactors, the response to revaccination would be even more modified and occur even earlier, than in the latter, i.e. areas of redness and oedema, reaching their maximum within the first 3 days then regressing to normal, without scar formation.

To assert, however, that such a reaction is indicative, solely and absolutely, of immunity to small-pox is quite erroneous, as was proved during the outbreak. When considering reactions, maximal within 72 hours of insertion other factors arise which must be taken into consideration.

(A) Trauma. (B) Sensitisation phenomena. (C) The initial signs of an early vaccinoid reaction.

Trauma. It is common knowledge that redness and swelling can be produced locally in response to the trauma of a simple incision. Such reaction occurs within 72 hours.

Sensitisation./

Sensitisation. Allergy to foreign protein is well-known and the Mantoux and Schick tests are examples of intradermal tests which require such a control.

In 1933 Craigie and Wishart investigating human skin sensitivity to washed, killed suspensions of vaccinial elementary bodies showed that when such a preparation was inoculated intradermally, into a previously vaccinated individual, an early reaction occurred within 3 days, whereas in an unvaccinated subject no such response could be elicited, i.e. a true allergic response caused by sensitisation to the foreign protein of previous vaccination.

Sensitivity and Immunity are not the same.

Early Vaccinoid Signs: Furthermore, within the first 72 hours of inoculation, the appearance of a raised slightly indurated areola might well be the first signs of an early vaccinoid reaction, which would increase the difficulties of differential diagnosis.

It will be appreciated, then, that an "Early (or "Immediate") Reaction can be due to, one, two or even all three factors. Leake (Pub. Health Rep. Wash. 1927 revised 1946) suggests that vaccine lymph weakened by time and temperature can also produce identical results.

I repeated the revaccination of 121 "Early" Reactors in my charge. Ample proof was available of the potency of the vaccine and daily inspection excluded early vaccinoid results. As a traumatic control, a/

a simple scratch incision, identical in length and depth, was made above the revaccination. It was most unfortunate that supplies would not permit the use of heat destroyed lymph as an allergic control. As before, each produced an area of redness and swelling, reaching its peak within the first 3 days and gradually regressing to normal, in about 7 days. In the vast majority of cases it was easy to distinguish by contrast, between the revaccination and trauma. (Photographs A & B in Appendix 2 well illustrate this.)

In the absence of an allergic control it was not possible to differentiate between pseudo and true reactions. Even if this had been available I very much doubt if differentiation could have been conclusive in all cases, if one remembers that in the great majority of cases, reactions, maximal in the first 72 hours, usually involve a small area. Even Leake who claims that a definite immune reaction exists, admits that sensitisation reactions indistinguishable from it occur, and the fact that such a reaction may be given by heat destroyed vaccine lymph, indicates that, at least, part of the visible phenomenon, called by him, the Immune Reaction, is due to this inert material.

Some authorities consider it unsound to regard any "Early" reaction, as of itself, safe evidence of immunity or to accept it as a successful vaccination i.e. Anything short of vesiculation is considered unsuccessful.

Ricketts, the one authority who has stood the test of time, more than any others, as long ago as 1908 stated, "short of a definite vesicale, the only evidence which should be accepted as indicative of success is a circumscribed deep-seated, indurated swelling of the skin under the seat of inoculation, developing about 3 days after the operation, and such a result should be confirmed by at least one subsequent inoculation."

In viewing the vaccination states of the small-pox cases for evidence supporting one or other of these contentions it will be noted that there were 12 patients with early reaction. In the 8 patients who showed "doubtful early" results, inoculation had been performed within the 12 days incubation period. Two of the remainder had been revaccinated 12 and 14 days prior to the onset of signs whilst the remaining 2 had been inoculated some months before. As the 8 results were doubtful, too much importance must not be placed on them, although successful vaccination has been recorded in an individual incubating small-pox. (Ricketts produces photographic evidence of this in his book and the Edinburgh outbreak produced another example.)

Even accepting Ricketts contention that immunity commences with the appearance of the local reactions the four remaining cases displayed early reactions before/

before contracting the infection. It therefore implies that these early reactions were not "immune reactions". Furthermore the same lymph was used to revaccinate the R.A.F. officer, who later contracted the disease, and 9 nursing orderlies, who at one time or another, attended him. All showed early reaction which appeared indistinguishable, yet he was not immune and they were.

One concludes therefore that the findings of the outbreak support the view that an "Early" (or "Immediate") Reaction is not, of itself indicative of an immune state, and if such a visible phenomenon as an Immune Reaction really does exist, it cannot be distinguished, with certainty, by appearance, from reactions due to factors not related to immunity.

No Reaction.

No reaction whatsoever to vaccination was sufficiently uncommon as to suggest failure in technique, non-viable lymph or failure to view the results at the proper time.

Sequelae of Vaccination.

Amongst the 4000 odd R.A.F. personnel, there is no record of the appearance of any non-specific rashes consequent upon vaccination. This is not altogether unexpected as the incidence of such rashes in a mixed population has been assessed variously from 1 in 5000 to/

to 1 in 9000, with females, at least equally, if not more, affected. In a population of about 30,000 it is not unlikely that cases did occur, possibly fleeting in character, as none were notified.

No case of Generalised Vaccinia was seen.

Post-Vaccinal Encephalitis is more liable following primary vaccination, after the age of 10 years. It was estimated in the Edinburgh Outbreak of 1942 that the incidence of this condition was 1 in 6300, after primary inoculation but only 1 in 65,900 in those revaccinated.

Considering that the population on Gibraltar was already highly protected, it is not surprising that no case of post-vaccinal nervous disease occurred. The only nervous case of virus origin about this time, was an R.A.F. officer with Acute Polio-encephalitis who was left with typical flaccid paralysis. He had been a contact of Acute Poliomyelitis, in the Azores. Four months previously he had been revaccinated.

<u>The Relationship of Vaccination to Immunity</u>.

Prior to the War, Variola major was not a frequent visitor to this country, and there was a tendency amongst medical practitioners, not in contact with the disease to exaggerate the capacity of vaccination to protect against small-pox.

Within limits, this capacity is incapable of exaggeration,/

exaggeration, as for a time, an individual successfully vaccinated, or revaccinated, acquires an immunity so complete as to prevent him contracting the disease. The medical attendants of the Cases well illustrate this. The difficulty arises in the assessment of the duration of this Absolute Immunity.

A few individuals acquire a life long immunity after successful vaccination in infancy, some after first revaccination. On the other hand, in rare instances immunity has been still impermanent after several successful vaccinations, while second attacks of small-pox have been known.

Case No.10 had been successfully vaccinated 4 yrs. previously yet died of small-pox. Case No. 13 showed 4 scars of infantile vaccination and during Post Office service was required to be reprotected periodically. His last successful revaccination was in 1942 and left a typical scar. Two years later he contracted a mild attack of discrete small-pox.

The mass of evidence suggests that the average duration of absolute immunity following successful vaccination or revaccination is about 4 yrs. Photographic proof of unmodified revaccination 2 yrs. after a previously successful vaccination is submitted in Appendix.2 Photo.C.

The minimum period of absolute protection, therefore, revealed by the outbreak, appears to be 2 yrs.

Whilst/

Whilst admitting that the Time Factor is probably the most important single factor in the determination of the amount of residual immunity another factor must be considered. I refer to the area of cicatrisation of the previous vaccination. In support of this statement reference is made to the Report by the Committee on Vaccination, 1928.

Revaccinating persons between the ages of 18-21 yrs. previously vaccinated only in infancy, the following relationship was shown between the total scar area of primary vaccination and the day of re-vaccination on which the maximum area of reaction was found.

Scar Area.	Under 500 sq. mm.	Between 500-1000 sq. mm.	1000 - 2000	Over 2000 sq. mm.
Ave. day of Max. Reaction	6.8 days	6.6 days	6.1 days	5.2

i.e. In primary vaccination, the greater the area of scar formation the higher the degree of residual immunity.

It was also shown with primary vaccination that the number of scars was of less significance than the total area of cicatrisation, the optimum being over 2000 sq. mm.

It will be appreciated that scar formation is merely/

merely a tangible, visible index not only of the intensity but also of the area of reaction to vaccination.

It follows then that if the duration of immunity varies with the total area of cicatrisation it must also vary with the area of reaction which originated the latter, i.e. the smaller the area of reaction the shorter the immunity lasts. If this is true, although a single insertion vaccination is likely to produce an area of reaction, equivalent to the optimum area of 2000 sq. mm., a single insertion Re-vaccination with its probable modified reaction is much less likely to do so. It is therefore recommended that the number of insertions for Revaccination should be increased to at least two insertions, ¾ inch long, whilst "Early" reactions should be repeated twice.

Although absolute immunity may be lost in as short a period as 2 yrs. partial residual immunity may remain for years, following primary or revaccination. Where present it tends to modify small-pox in a two-fold manner, 1. by reducing the severity of toxaemia and 2. by modifying the numerical density of the small-pox eruption. The following analysis of the Gibraltar cases well illustrates these features.

Vaccination State	Total.	Type of Disease.			Severity.		Deaths	Mortality Rate.
		Haem. Con-fluent	Confluent	Discrete	Severe	Mild		
A. No Evidence whatsoever of Successful Vaccination (as indicated by Scar formation)	4	3	0	1	3	1	2	50%
B. Doubtful Evidence of Successful Vaccination.	6	1	1	4	2	4	2	33.3%
C. Evidence of Successful protection. Once only - in childhood or later.	3	0	2	1	3	0	2	66.6%
D. Evidence of Successful Protection in Infancy and recaccination at the Outbreak.	5	0	0	5	0	5	1	20%
E. Evidence of Successful Protection in infancy and revaccination at	5	0	0	5	1	4	1	20%

It will be seen that the higher the degree of residual immunity, indicated by the number of vaccinations, the higher incidence of discrete types, the greater the number of mild cases and the lower the mortality rate.

In table C, a case No.8) will be noted, discrete in type but severe in toxicity. This man was successfully vaccinated in childhood, and illustrates the fact that with diminishing immunity, protection against toxaemia tends to be lost before that which tends to modify the numerical density of the eruption.

SUMMARY:

1. An Outbreak of Variola Major is described.

2. Mass Vaccination stopped the Outbreak.

3. Successful Vaccination or revaccination protects against small-pox for a time.

4. The minimum period of Absolute Immunity to vaccination or revaccination appears to be 2 yrs.

5. In Small-pox, partial residual immunity tends to modify the numerical density of the Rash and the severity of toxaemia, and the latter immunity disperses earlier.

6. It is suggested that Residual Immunity is associated not only with a time factor but also with the total area of reaction of the previous vaccination or revaccination.

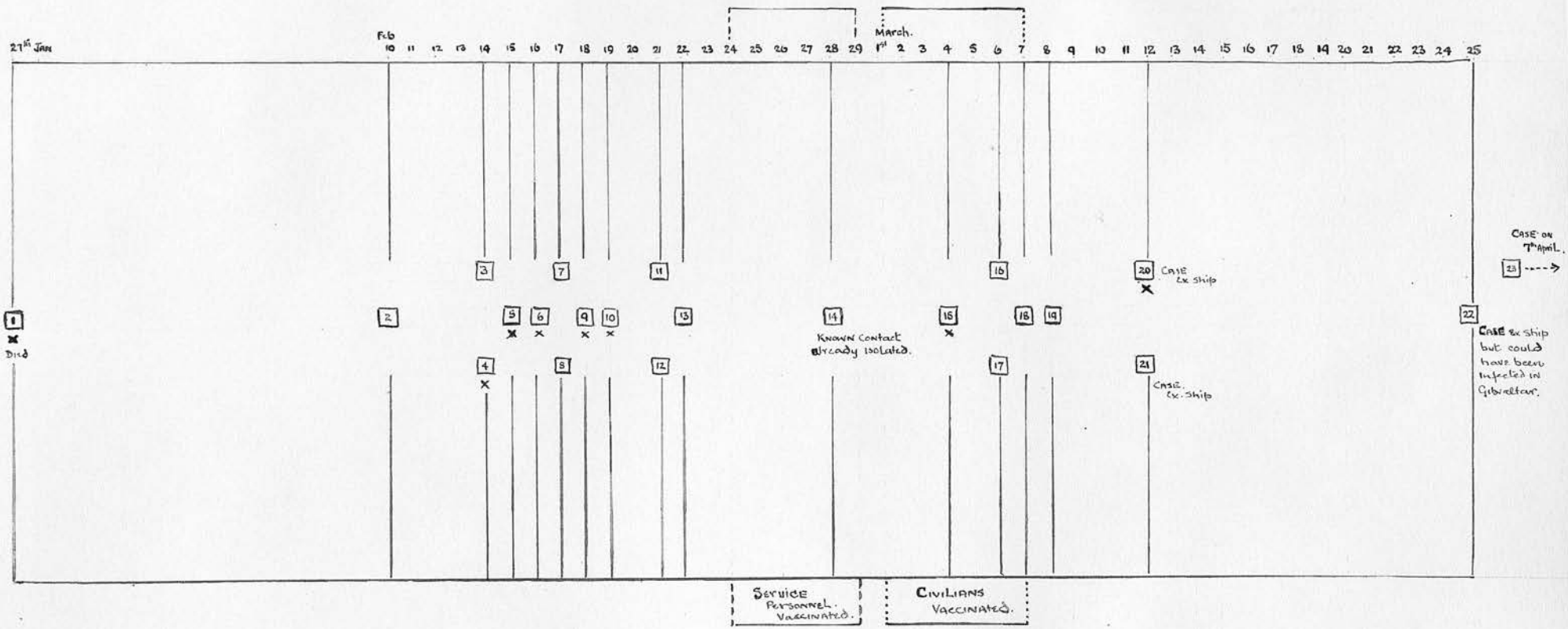
7./

7. Revaccination should consist of, at least 2 insertions ¾ inch long, and 1 inch apart.

8. If such a phenomenon as an Immune Reaction really does exist, it is indistinguishable by appearance from reactions due to factors not associated with immunity.

9. "Early" reactions should be repeated twice.

Smallpox Outbreak. Gibraltar. 1944.



Appendix. I.

Appendix 2.

Photo A

Showing scar of Original Vaccination 10 Feb 1941
Revaccinated (24 Feb 1944). Shows area of redness induration and swelling in contrast with simple control scratch situated above.
Photograph taken 72 hours after inoculation.

Photo B.

Photograph of the same arm as in A.
taken 7 days later
Scar of original vaccination (Feb 41) shows but all evidence of revaccination 10 days previously has now disappeared.

Appendix. 2.

Photo C

Shows scar of previous vaccination 31 Jan 42.
Revaccination (24 Feb 44) shows commencing
Vesiculation on the 5th Day.
The control scratch incision can be seen
above.

Photo. D.

Shows scar of previous vaccination March 41
Revaccination (24 Feb 44) shows Vesiculation
by the 5th Day.
The Control incision can be seen above.